sources may be integrated in order implement prospective observational research studies that answer complex research questions.

RESEARCH ON METHODS – Conceptual Papers

PRM132
WHAT ARE THE ROLES OF HEALTH ECONOMIC MODELS IN PRODUCT DEVELOPMENT?

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OBJECTIVES: Health economic models are widely used for drug evaluation during the post-approval and reimbursement process. However, similar models can also be used to inform objectives, decisions and designs earlier in the drug development process with the idea to optimize the potential future value to payers. This project assesses how an economic heart failure (HF) model can facilitate the decision making process during the early stages of drug development. **METHODS:** A discrete event simulation is developed to track the events associated with disease progression of HF patients over 5 years. Patients are initially categorized into one of three health states based on their HF status: in-hospital, 30 days post-discharge and > 30 days post-discharge. To capture movement in the model, the time to hospital discharge, re-hospitalization and death are generated based on each patient's current health state and the event rates taken from available literature. The model is used to identify baseline levels of risk, a range of potential prices or the required drug efficacy that the drug candidate needs to meet in order to be cost-effective compared to standard care. **RESULTS:** By way of illustration, we considered a patient with baseline mortality risk of 0.1% and a 0.2% readmission rate per day. If treatment costing $1 /day is provided to patients outside of hospital, a mortality reduction of at least 12% is needed to meet a $25,000/QALY threshold. For a higher risk population, the treatment can remain cost-effective at either a higher price or lower clinical efficacy. **CONCLUSIONS:** This study demonstrates that health economic models are useful to determine the acceptable ranges of baseline risk, efficacy, and price to assess the potential value of future drug candidates.

PRM133
USING SURROGATE ENDPOINTS FOR HEATH ECONOMIC ANALYSIS: WHAT IS THE ROLE OF STATISTICAL VALIDATION?

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OBJECTIVES: To explore the appropriate use of surrogates within an economic modeling framework, compared to the statistical approaches of validating surrogates. **METHODS:** We reviewed the statistical literature on validating surrogate endpoints. Published statistical approached to validating surrogate endpoints include those described by Prentice and Buyse. We explore the use of these statistical approaches to validation in the context of health economic models where surrogates are used (a) predict final outcomes, and (b) as endpoints for stopping rules and patient access schemes. **RESULTS:** Given regulatory trials powered on surrogate endpoints, economic modeling often requires the use of surrogate endpoints to estimate the impact of treatment on final health outcomes of interest to reimbursement agencies. This requirement occurs even when there is no statistical validation of the surrogacy relationship, or when the surrogate fails a formal statistical validation. As a consequence we argue that the appropriate focus for economic modeling is on the appropriate propagation of uncertainty in the estimates of the effect of the surrogate on final health outcome and the avoidance of bias due to multiple testing rather than the formal testing of validity. This includes the use of stopping rules that are designed to improve cost-effectiveness estimates for patient access. **CONCLUSIONS:** The approach to surrogacy in reimbursement is necessarily different to that in a regulatory environment. We outline a general estimation approach based on appropriately characterizing uncertainty in the surrogacy relationship rather than the formal statistical testing of surrogate validity as the appropriate focus of reimbursement models.

PRM134
STANDARDIZING CRITERIA FOR COGNITIVE ASSESSMENT OF PAPER-TO-ELECTRONIC EQUIVALENCE OF PROS

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AIMS: Use of electronically administered outcome measures is increasing in clinical trial data collection. The 2009 ISPOR ePRO Task Force Report recommends cognitive assessment as sufficient evidence of equivalence when only minor changes have been made to the measure. No consensus exists, however, for how cognitive assessment results should be evaluated to determine if equivalence has been established. **METHODS:** Existing literature around equivalence assessment for PROs was combined with firsthand experience in conducting over 500 cognitive interviews aimed at assessing paper and electronic equivalence of 55 different PRO instruments. Using these two resources, we developed suggested criteria to cognitively assess equivalence between the two modes, and present a practical process for meeting these criteria. **RESULTS:** The criteria for determining equivalence between paper and ePRO formats should focus primarily on whether or not the ePRO is likely to produce data substantially different if administered via one method versus the other. To determine whether such a risk to ePRO data exists, we propose a three-step process for interpreting cognitive interview responses. 1) Determine whether a patient perceives a cognitive difference between paper PRO and ePRO, and whether that difference represents a variation in the understanding of the item or simply a recognition of different appearance; 2) Determine whether any difference in patient understanding has a meaningful impact on their response to the item, and 3) determine whether or not that difference presents a significant risk to the data that justifies modification of the ePRO. **CONCLUSIONS:** In the years since the ISPOR ePRO Task Force issued their recommendations, data capture technology has continued to develop while clarity on methods to evaluate the cognitive impact of this technology have lagged. The steps we present provide a standardized system for ensuring that ePROs measure what is intended and the risk to research data is minimized.

PRM135
RISKS, IMPACTS, AND MITIGATION OF MISSING EPRO DATA ON CLINICAL TRIALS

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OBJECTIVES: Although missing and incomplete responses in ePROs can be minimized through risk assessment and mitigation plans, missing data can have varying implications on clinical trials. This conceptual paper assesses the impact of missing ePRO data to the trial, taking into account the phase of the trial and intended use of the data. **METHODS:** Common uses for data gathered via ePRO instruments and diaries are reviewed. An assessment of the impact of different levels of missing data and associated risks with analyzing data is also performed. **RESULTS:** Data gathered via ePRO are frequently used to support primary/secondary trial endpoints. They are also commonly used for exploratory purposes, allowing sponsors to gather preliminary information to guide the planning of future trials. Types of data collected may include study medication usage for study drug reconciliation reasons, symptom presence or severity to determine eligibility for trial participation, and responses over time to indicate improvement or worsening of the symptom/disease. Each data use is assessed for risks to the analyzability of the data associated with different levels of missing data. For example, in projects with ePRO responses used to support primary/secondary endpoints overall project risk is low when compliance rates are high (e.g. 90-100%). As compliance rates drop to <80%, bias introduced in the results increases, quality of the data decreases, and risks that the data may not be able to be used in the analysis rises. Impacts could include a need to recruit additional patients or that the trial may need to be re-run. **CONCLUSIONS:** Impacts of missing data on clinical trial analysis vary depending on the intended use of the data. It is important to understand the impact of missing data to the project so that an appropriate plan can be decided upon and included in the protocol.

PRM136
METHODOLOGICAL AND OPERATIONAL CONSIDERATIONS IN CONDUCTING RETROSPECTIVE MEDICAL CHART REVIEW STUDIES IN HOSPITALS AND MEDICAL CENTERS IN EMERGING MARKETS

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OBJECTIVES: Retrospective medical chart reviews are an increasingly valuable source of data for clinical, treatment patterns, and outcomes research, particularly in emerging markets where availability of databases for secondary analysis is limited. This abstract aims to describe methodological and operational considerations that sponsors and researchers should be aware of prior to and during the undertaking of chart review studies in these markets. **METHODS:** Key considerations for executing chart review studies in hospitals and major medical centers from study conception through the completion and quality review of data collection were identified and summarized. **RESULTS:** After identification of research objectives and target countries/markets for research, thoughtful consideration of site selection (single or multi-site/country, local investigator interest and availability), data availability (nature, comprehensiveness, and quality of existing medical records), and patient selection (sampling design, specificity of inclusion/exclusion criteria) form the basis for implementing a successful chart review. Study design steps may be taken to optimize performance, for example: careful consideration of how inclusion/exclusion criteria will impact patient recruitment given the rarity of the study condition (data on this may be limited); assessing feasibility of data collection instrument completion via piloting and prior local experience; standardization of terms and definitions to ensure cross-site comparability. Additional operational considerations include meeting varied requirements for obtaining national/state and local ethics approval in multi-country studies, use of electronic data capture given variation in information technology infrastructure across study sites, and impact of workday/cultural traditions on recruitment/ timelines. **CONCLUSIONS:** To maximize the opportunity for successful medical chart review studies in emerging markets, review and assessment of operational feasibilities in the target research areas, appropriate tailoring of study objectives, engagement of local investigators and site staff, and continuous oversight of data collection and quality control processes are essential.

PRM138
A FRAMEWORK FOR ANALYSING TREATMENT SEQUENCES: INCORPORATING TIME DEPENDENT TRANSITIONS THROUGH PARTITIONED SURVIVAL ANALYSIS

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It is often the case that cost-effectiveness models need to consider the sequence of treatments in a treatment algorithm. Since traditional state transition Markov models have an inherent memoryless property, time dependency in time to event analysis cannot be incorporated in this modelling framework. This has been used as a rationale for moving to individual level simulation models to handle treatment sequences. However, individual simulation models increase the computational burden of a model, particularly when it comes to undertaking real-time probabilistic sensitivity analysis to characterize uncertainty. Therefore, adifferent approach to modeling treatment sequencing should be examined. In this paper, we discuss a novel approach to analyzing sequencing models that allow time dependency in the time to event analysis within a cohort model framework,thus avoiding the disadvantages of resorting to individual simulation. Typically parametric survival models can be used to characterize time to event. This may be time to overall survival or time to progression in cancer modelling, or time to treatment failure / treatment switching in oncology. We illustrate the approach using parametricWeibull models, although in principle any parametric survival model could be used. We show how

the framework is flexible enough to capture treatment effects that vary by line of therapy, and we demonstrate how appropriate discounting to allow for differential timing can still be made. We believe that the framework illustrated in this paper has wide applicability to sequencing models in many disease areas, most notably oncology and rheumatology where such sequencing models are common. We demonstrate the flexibility of the approach and show how time dependency can be incorporated at any sequence of the model without having to resort to individual patient simulation.

PRM139

A COMPREHENSIVE ECONOMIC AND PRICING MODELING FRAMEWORK FOR UNDERSTANDING ORPHAN DRUG DEVELOPMENT

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Rare diseases provide a perplexing problem for reimbursement agencies. Orphan drug development is often incentivized by government entities. Despite these incentives, reimbursement at a viable level is not assured, and recent efforts by reimbursement bodies are changing the reimbursement paradigm substantially. Value-based pricing agreements, which link the price of the drug to the value achieved, is one such effort. However, demonstrating value for an orphan drug remains challenging. To better understand the potential value and therefore pricing of orphan drugs, we developed a comprehensive model to evaluate the pricing, economics, reimbursement, and market strategy (PERMS) specifically for these drugs. The interactive simulation model was developed to combine evidence on development costs, cost-effectiveness, treatment pathways, improvements in quality of life, and market share. The PERMS model was designed to evolve alongside the drug development process, incorporating new parameters and data as they become known. Extensive sensitivity analyses are performed to highlight the substantial uncertainty in disease prevalence and costs of the diseases. An interactive interface is developed for users to examine how changes in model input values affect outcomes of interest. In this presentation, we will describe the primary elements of the PERMS model, demonstrate how the results may vary across subpopulations and illustrate the potential value of new drugs. Concepts will be illustrated through the use of real-world examples such as graft-versus-host disease (GVHD); a major complication of stem cell or bone marrow transplantation that has significant prognostic implications in the setting of a rare resource. This presentation will illustrate how a holistic view through simulation modeling can be useful and informative for understanding disease burden and potential reimbursement levels and making a decision to proceed to the next phase of drug development.

PRM140

CONCEPTUAL MODEL DEVELOPMENT AND PROS FOR NON-DIABETIC PERIPHERAL NEUROPATHIC PAIN

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OBJECTIVES: To demonstrate how a conceptual model of symptoms of non-diabetic peripheral neuropathic pain, impact on quality of life and tolerability of treatments helps to select patient reported outcomes (PROs) in clinical trials. To show that the selected PROs measure what is expected. **METHODS:** A literature review and interviews with 4 clinical experts were conducted to identify the PRO measurement concepts related to symptoms and impacts of highest importance and relevance to non-diabetic peripheral neuropathic pain patients. The mechanism of action of treatments available and in development were also included in the conceptual model. Based on this information, available instruments were evaluated to assess if measures focusing on emerging, central concepts were available and of relevance to a planned Phase IV study. **RESULTS:** Based on the literature review and expert interviews, pain was the predominant symptom concept. The most predominant impact concepts were difficulty with sleep quantity and quality. Available treatments suggested detrimental impact on cognition and local treatment-related pain. Instruments that seem to measure the central concepts were numerical pain rating scale scale (NPRS), MOS-Sleep and MOS-Cog. Furthermore the Treatment Satisfaction Questionnaire for Medication (TSQM) was assessed in order to be able to measure treatment satisfaction comparing different medications Results of the chosen PROs included in a Phase IV study with patients with non-diabetic peripheral neuropathic pain seem to show that they are able to measure the concepts they were selected to assess. **CONCLUSIONS:** The FDA PRO Guidance states that measures should be conceptually valid as they relate to the disease being studied, meet a threshold of psychometric soundness, and be relevant to patients. This research represents an important step toward establishing the PROs that could be used in studies with patients with non-diabetic peripheral neuropathic pain.

PRM141

MODELING ALL-CAUSE MORTALITY IN HEALTH ECONOMIC MODELS

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The estimation of life-years is an important component of many health economic models and this outcome is often required by health technology assessment agencies in the evaluation of health care technologies. Life-years are often obtained by adjusting the country-, age-, and gender-specific all-cause mortality, which considers all deaths in a population regardless of the cause, to account for additional deaths due to a specific disease (i.e., the disease-specific mortality). Properly modeling all-cause mortality and knowing the uncertainty associated with the estimates (if estimated) is therefore an important step in building a health economic model. The report of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Modeling Good Research Practices Task Force recommends modeling all-cause mortality non-parametrically based on life table data. This method uses the life table data directly to derive an empiric distribution of death times. Additionally, parametric survival analysis may be used to fit life table data. This method may be more flexible, avoiding the need to look up mortality hazards directly from life tables, requiring fewer parameters, and possibly saving computation time. Typically, this method is carried out by linearizing specific parametric survival distributions and using regression analysis on data from the life table to obtain estimates for the parameters of the distribution. Although this type of analysis is fairly straightforward, the estimates of the uncertainty around the parameters are inaccurate. A new method of obtaining these parameters, which involves simulating individual death times from the life table data and using maximum likelihood estimation to obtain the needed parameters, may be considered when modeling all-cause mortality. Utilizing the number of individuals at risk, this method may provide more accurate estimates of parameters and their uncertainty. The implementation, appropriateness, challenges, advantages and disadvantages of these three techniques when modeling all-cause mortality in health economic models will be discussed.

PRM142

JOINT BAYESIAN NETWORK META-ANALYSIS FOR EVENT COUNTS AND HAZARDS – COMPARISON OF METHODS AND IMPLEMENTATIONS

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Networks of treatments summarize all available information about the relative effectiveness of several treatments, also if both direct and indirect evidence needs to be combined[1]. For clinical trials with survival results, some will have been reported based on numbers of patients with event, and some based on the hazard ratio. A common scale for mapping the observed effects has been proposed[2]. Treatment contrasts would then be estimated through Bayesian methodology based on Markov Chain Monte Carlo (MCMC) simulation. Similar problems arise for trials with binary outcome. We investigate one example from pulmology and compare two implementations of the MCMC method, WinBUGS and SAS® PROC MCMC. Moreover, we investigate a deterministic-numerical approximation to the distribution of treatment contrasts, the integrated nested Laplace approximation (INLA) method. Of particular interest here is the goodness of the approximation, as the example dataset includes only small numbers of trials, patients and events. We show how to condense graphically the complex pattern of multiple treatment comparisons. We conclude with remarks on model selection, goodness-of-fit and the Deviance Information Criterion (DIC).

PRM143

PRACTICAL ISSUES WHEN CONDUCTING NETWORK META-ANALYSES WITH A LIMITED NUMBER OF STUDIES

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OBJECTIVES: Meta-analysis is being conducted extensively in part due to requirements from health care decision-making agencies. Meta-analysis techniques continue to develop, and software now exists to model networks using Bayesian or frequentist approaches with study effects treated as fixed or random. The non-model based anchored indirect-treatment comparison (AIC) method is also suitable for making pairwise treatment comparisons. However, practical issues emerge particularly when the network is comprised of a limited number of studies. Of special interest is the situation where a star network contains only one trial for a given treatment comparison. Our goal was to investigate the performance and interpretation of different meta-analysis methods when few studies are available. **METHODS:** Example star networks anchored by placebo were created for binary endpoints with varying proportions and sample sizes. Generalized linear mixed models were fitted using PROC GLIMMIX in SAS with a random study effect. Results were compared to the AIC method as well as analogous Bayesian models using WinBUGS. **RESULTS:** Estimated odds ratios were examined to identify patterns among methods. If placebo effects were largely different across individual trials, differences between methods varied depending on effect sizes and sample sizes. If placebo effects were similar, the frequentist random-effects model was not able to estimate a random study effect and it was reduced to a fixed-effect model (similar to the AIC). **CONCLUSIONS:** The limitations of conducting a meta-analysis with a small number of trials should be understood regardless of the methodology used. In the special case of a star network with only one trial per treatment comparison, the differences between methods depend on the underlying evidence. The implications for interpretation will be discussed.

PRM144

EXPLORING THE IMPACT OF STRUCTURAL UNCERTAINTY IN PARTITIONED SURVIVAL MODELS FOR ONCOLOGY

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OBJECTIVES: Economic evaluations in oncology built using partitioned survival analysis do not permit analysis of the post-progression period separately from the progression-free period. Moreover, when the outcomes are not complete at the time of the analysis, the benefits experienced by patients in the clinical trial used to inform the model are assumed to continue for the duration of the model due to extrapolation of the trial data using one set of parametric curves. The objective of this study is to present and contrast possible methods to address the structural uncertainty in the incremental effects and the cost-effectiveness estimates derived from partitioned survival models. **METHODS:** Options for addressing the long-term benefits in partitioned survival models are explored using a hypothetical economic model with three states (progression-free, progressed disease, and death). The methods include the standard approach of projecting treatment group PFS and OS outcomes using parametric survival curves, using time-varying hazard ratios to modify the relative benefits between treatments, calculating and modifying treatment-related Markov probabilities following progression in the cohort,